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(54) Title: ANTIDIARRHEAL COMPOSITION AND METHOD

(57) Abstract

The present invention provides a composition and method for treating diarrhea and related conditions. The antidiarrheal composition of the present invention comprises an admixture of one or more nutritional substances, a synthetic fiber, and electrolytes so the electrolyte requirements for rehydration are met in an orally palatable formulation. Optionally, a *Lactobacillus sp.* can be added to the antidiarrheal composition.

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ANTIDIARRHEAL COMPOSITION AND METHOD

Technical Field

The present invention relates to an antidiarrheal composition and a method for treating diarrhea and related conditions. More particularly, the present invention provides a palatable composition for treating diarrhea in a human or an animal comprising one or more nutritional substances, a synthetic fiber, and an electrolyte admixture. Optionally, a *Lactobacillus sp.* can be added to the antidiarrheal composition.

Background of the Invention

As used herein, the term "diarrhea" is an increase in stool frequency with a concomitant decrease in stool consistency. The term "secretory diarrhea" is an increase in the volume of water in the stools due mainly to increased secretion of electrolytes and consequently water. The term "nutritional substance" as used herein includes, but is not limited to, carrots, maize, millet, sorghum, carob, rice, rice flour, rice water, mashed potatoes, and short-chain glucose polymers or admixtures thereof.

Diarrhea is a common and often debilitating disease in children and adults. In developing countries, diarrheal diseases

are the largest single cause of death among infants and children. In developed countries, diarrheal disease causes significant morbidity and unnecessary mortality. In the United States, for example, acute gastroenteritis ranks second only to the common cold in frequency, accounting for more than 3 million (3%) of pediatric office visits. Acute diarrheas are caused by, among other things, viruses, bacteria, and parasites. The onset of acute diarrhea is usually within 2-3 days of infection but can be immediate and its clinical features are fluid diarrhea, sometimes with blood and mucus, and acute weight loss. Diarrhea can cause dehydration, electrolyte imbalances, acid-base disturbances and, in severe cases, can result in death. The interrelationships among gastrointestinal infection, nutritional status, and growth and development during infancy and childhood are well established. The key role of diarrheal disease in the downward spiral leading to malnutrition, impaired immune host defense, and increased susceptibility to a further intestinal infection is well established for bacterial, viral, and parasitic diseases.

Diarrhea occurs when there is an imbalance between the processes for intestinal absorption and secretion of water. This imbalance may be caused by either decreased absorption or increased secretion or a combination of both. Because the transfer of water across the intestinal mucosa is a passive consequence of movements of solutes, both decreased absorption and increased secretion of water are associated with changes in transfer of solutes, which can be either organic substrates or electrolytes. A large number of agents are capable of stimulating intestinal secretion. These agents include bacterial enterotoxins, intralumenal metabolites, hormones, neurotransmitters, and other endogenous substances.

Acute gastroenteritis, which may be regarded as an acute infection of the gastrointestinal tract, is usually a self-limiting, short illness, lasting up to a week or ten days. The

majority of cases are managed by oral rehydration therapy and only those with severe dehydration require intravenous fluids to supplement body water.

Early use of oral rehydration salt solution can correct and prevent the progress of the dehydration that can occur in acute childhood diarrhea. Oral rehydrating solutions can be regarded as an effective means of restoring the fluid and electrolyte losses in diarrheas of various etiologies. Glucose-linked enhanced sodium and water absorption from the small intestinal lumen is largely intact during acute diarrhea of diverse etiology and form the scientific basis of oral rehydration therapy. Conventional oral replacement therapy consists of glucose, salts, and water.

Because this therapy does not result in reductions in stool frequency, in stool volume, or in duration of the diarrhea, users often do not continue the therapy through the episode of diarrhea. Instead, they resort to the use of antidiarrheal medicines and antibiotics which, themselves, may lead to chronic diarrhea and malnutrition. Antimicrobial agents may themselves cause diarrhea and pseudomembranous colitis. In addition, such medications are expensive and are not readily available in underdeveloped areas of the world.

Cereal base oral replacement therapy has been used to improve home therapy of diarrhea to decrease the number of referrals to treatment centers. Constraints of cereal based oral replacement therapies include need for cooking prior to use, fermentation and bacterial overgrowth, and difficulty in making a ready to use packaged product.

In patients with chronic diarrhea and superimposed malnutrition, correction of both the diarrhea and the nutritional deficit is of major importance. Dietary starches are an important source of caloric intake. However, their inclusion in food based

oral rehydration solutions can create a significant osmotic load in a dehydrated child with disturbances in fluid and electrolyte balance. Oral replacement therapies cannot greatly exceed plasma osmolality without risk of increased diarrhea.. Inclusion of starches in oral rehydration solutions can be especially detrimental in children under six months of age in whom pancreatic amylase, the enzyme which digests starch, is not fully developed. Starch in oral replacement therapies, while providing needed nutrition, can exacerbate the underlying diarrheal disorder. What is needed is a high caloric density diet which can deliver large amounts of glucose in digestible form to the intestinal absorptive cell transporter, but which has low osmotic activity.

Glucose polymers are useful for increasing available glucose without increasing significantly osmotic activity in the intestinal lumen. In fact, short chain glucose polymers are superior to D-glucose in correcting abnormal water and electrolyte transport Short-chain glucose polymers of rice comprising two to nine glucose units are hydrolyzed and absorbed in the small intestine faster than isocaloric D-glucose. Other sources of glucose polymers include, among others, corn, sorghum, and tapioca.

In children, traditional treatment of diarrhea has mandated withdrawal of food followed by gradual reintroduction of food after cessation of the diarrhea. However, continued feeding may act to decrease the diarrhea and to improve nutrition.. Because milk and milk products are an essential source of nutrients in children, milk tolerance is important in the management of their diarrhea.

Lactobacillus acidophilus is a therapeutically beneficial strain of bacteria which is a component of the normal intestinal flora of most healthy human beings. Generally, the

normal intestinal flora contains in excess of 10^{11} colony forming units (CFU) of lactobacilli. Certain strains of *Lactobacillus acidophilus*, when ingested by humans or animals produce beneficial effects on gastrointestinal function and provide resistance to gastrointestinal colonization by pathogenic microorganisms. One of these, the GG strain of *Lactobacillus acidophilus* (*Lactobacillus* GG) is the subject of United States Patent No. 4,839,282 to Gorbach et al., which is incorporated herein by reference. The strain of Lactobacillus that is described in U.S. Patent No. 4,839,282 has been renamed *Lactobacillus casei rhamorum*, strain GG. As used herein, the term "*Lactobacillus* GG" shall mean the strain of Lactobacillus described in U.S. Patent No. 4,839,282.

The *Lactobacillus* GG promotes carbohydrate digestion and aids in protein digestion. The sugars, amino acids, and peptides produced by the action of the *Lactobacillus* GG provide nutrition and promote rehydration via the sodium-solute intestinal epithelial cell transporter. Furthermore, in malnourished children, diarrhea may alter the intestinal microflora. *Lactobacillus* GG is able to colonize the human intestine and to produce antimicrobial substances which control proliferation of gram-negative and gram-positive organisms. For these reasons, *Lactobacillus* GG, administered as a component of an oral replacement regimen can accelerate recovery from diarrhea.

Polycarbophil is a polyacrylic acid cross-linked with di-vinyl glycol. It is a pharmacologically inert substance which has the capacity to bind free fecal water. It acts to reduce stool frequency and stool volume. Orally administered, polycarbophil exerts its most marked hydrosorptive action only on reaching the slightly acid or alkaline medium of the small intestine and colon.

U.S. Patent No. 2,798,053 to Brown, entitled "Carboxylic Polymers", suggests the usefulness of carboxylic polymers in the treatment of various disorders of the human and animal gastrointestinal tract (Column 1, lines 70-71) including their use as bulk laxatives (Column 1, lines 68-69). This patent is directed to the polymerization of carboxylic-type monomers and the production of carboxylic polymers.

U.S. Patent No. 3,655,869 to Wharton et al., entitled "Treatment of Diarrhea Employing Certain Basic Polyelectrolyte Polymers", describes a method for the treatment and prevention of diarrhea by oral administration of a basic polyelectrolyte polymer. This patent discloses the effectiveness of certain basic polyelectrolyte polymers in adsorbing intestinal bacteria.

U.S. Patent No. 4,164,568 to Bywater, entitled "Oral Scour Formulations with Citrate", discloses a veterinary composition for oral treatment of diarrhea in animals.

U.S. Patent No. 4,419,369 to Nichols et al., entitled "Protein Mineral Dietary Module", discloses a dietary protein mineral module for use in the treatment of chronic diarrhea of infancy.

U.S. Patent No. 4,869,908 to Kirschner et al., entitled "Fibre Formulations", discloses nutritional or therapeutic compositions being administered in conjunction with dietary fiber substances.

Japanese Patent No. J5 9065-016-A to Nisshin Flour Mill KK, entitled "Composition for Preventing and Treating Diarrhea in Animals", discloses the use of sodium polyacrylate and an insoluble mineral adsorbent to remedy diarrhea in animals.

What is needed is an effective oral replacement therapy based on ingredients which reduce stool frequency and stool volume and, at the same time, are nutritionally valuable. The oral replacement should be palatable, and be easy to administer in unit dosage form. In addition, the oral replacement therapy for treating diarrhea should be acceptable for use outside the hospital or doctor's office without the need for trained medical personnel.

Summary of the Invention

The present invention provides a composition and method for treating diarrhea and related conditions in humans or animals. The present invention can be used to treat adults or children.

The antidiarrheal composition of the present invention comprises an admixture of one or more nutritional substances, a synthetic fiber, and an electrolyte admixture so the electrolyte requirements for rehydration are met in an orally palatable formulation. This admixture can be prepared as a sterile composition. Optionally, an effective concentration of *Lactobacillus acidophilus* can be added to the antidiarrheal composition of the present invention. The antidiarrheal composition can be stored conveniently until used and can be administered in unit dosage form which is more convenient and safer than currently used methods. The present invention can be premixed and dehydrated either by desiccation or lyophilization. When used, the dehydrated composition need only be rehydrated and administered to the patient orally.

Accordingly, it is an object of the present invention to provide an antidiarrheal composition useful in the treatment of diarrhea, particularly but not exclusively in children.

It is another object of the present invention to reduce stool output.

It is another object of the present invention to provide a sterile antidiarrheal composition.

It is another object of the present invention to provide a readily available antidiarrheal composition.

It is another object of the present invention to provide a composition and method useful for fluid and/or electrolyte replacement.

It is another object of the present invention to provide a readily available antidiarrheal composition that is effective in treating traveller's diarrhea.

It is another object of the present invention to provide a readily available antidiarrheal composition that is effective in treating antibiotic-associated diarrhea.

It is another object of the present invention to provide a readily available antidiarrheal composition that is effective in treating diarrhea caused by *Clostridium difficil.*

It is another object of the present invention to provide a ready to use antidiarrheal composition.

It is another object of the present invention to provide a treatment for oral rehydration.

It is another object of the present invention to provide a treatment for oral rehydration in HIV patients.

It is another object of the present invention to provide a pre-packaged antidiarrheal composition.

It is another object of the present invention to provide an antidiarrheal composition in unit dosage form.

It is another object of the present invention to provide an antidiarrheal composition for use in the home.

It is another object of the present invention to provide an antidiarrheal composition that will supplement lost electrolytes.

It is another object of the present invention to provide an antidiarrheal composition that will provide high caloric density with a small increase in osmolality.

It is another object of the present invention to provide an antidiarrheal composition that will provide resistance to gastrointestinal colonization by pathogenic organisms.

It is another object of the present invention to provide an antidiarrheal composition that will reduce gastrointestinal side effects of antibiotic therapy.

It is another object of the present invention to provide an antidiarrheal composition that will aid in the digestion of milk and milk products.

It is another object of the present invention to provide a palatable antidiarrheal composition.

It is another object of the present invention to provide an antidiarrheal composition for use by children.

It is another object of the present invention to provide a prepackaged antidiarrheal composition which can be premixed and dehydrated so that the composition can be used after rehydration.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiment and the appended claims.

Detailed Description of the Invention

The present invention provides a composition and method for treating diarrhea and related conditions. The antidiarrheal composition of the present invention comprises one or more nutritional substances, a synthetic fiber, and an electrolyte admixture so the electrolyte requirements for rehydration are met in an orally palatable formulation. The present invention can be prepared as a sterile composition. The therapeutically useful bacteria *Lactobacillus acidophilus* can be included in the antidiarrheal composition of the present invention. The present invention can be stored conveniently until used and can be administered in unit dosage form which is more convenient and safer than currently used methods. The present invention is also useful for oral rehydration.

The nutritional substance that is a component of the composition of the present invention includes, but is not limited to, carrots, maize, millet, wheat, sorghum, rice flour, rice water and mashed potatoes or admixtures thereof. Of these, the preferred nutritional substance is rice flour or mashed carrots. The quantity of these nutritional substances that is preferred in the composition of the present invention is between 1 g/100 ml and 20 g/100 ml. The preferred quantity is between 3 g/100 ml and 10 g/100 ml.

The synthetic fibers that can be used in the antidiarrheal composition of the present invention includes, but is not limited to, acrylates and, more particularly, polycarbophil. The quantity of the synthetic fibers that is preferred in the composition of the present invention is between 0.05 g/100 ml

and 0.3 g/100 ml. The preferred quantity is between 0.08 g/100 ml and 0.2 g/100 ml with the most preferred concentration of synthetic fiber being approximately 0.1 g/100 ml.

The electrolyte composition of the antidiarrheal composition of the present invention comprises an admixture of sodium salt, chloride, citrate, potassium salt and bicarbonate. The salts can be either chloride or citrate. In addition, zinc salt can be added to the electrolyte admixture. It is to be understood that the exact concentration of each electrolyte is not critical to the present invention.

Another nutritional substance that optionally can be included in the composition of the present invention is short-chain glucose polymers derived from controlled hydrolysis of starches including, among others, rice, sorghum, corn, and tapioca. The preferred quantity of short-chain glucose polymers is between 0.5 g/100 ml and 25 g/100 ml. The most preferred quantity is between 2.5 g/100 ml and 5 g/100 ml.

Another component that can be included in the composition of the present invention is *Lactobacillus*.. The preferred strain of *Lactobacillus* is the *Lactobacillus casei rhamorum*, strain GG, although it is to be understood that other strains of *Lactobacillus* can be used in the present invention. The preferred concentration of *Lactobacillus* is between 10^6 CFU/100 ml and 10^{12} CFU/100 ml. The most preferred concentration is between 10^9 CFU/100 ml and 10^{10} CFU/100 ml.

In addition, glucose can optionally be added to the antidiarrheal composition of the present invention. The preferred concentration of glucose in the antidiarrheal composition of the present invention is between approximately 10 and 100 mM/L, with the more preferred concentration between approximately 20 and 75 mM/L. The most preferred concentration of glucose in

the antidiarrheal composition of the present invention is approximately 40 mM/L.

It is to be understood that the antidiarrheal composition of the present invention can be dehydrated to provide an easily stored and transported composition. The antidiarrheal composition of the present invention can be dehydrated either by submitting the liquid composition to lyophilization procedures which are well known to those of ordinary skill in the art or by desiccating the composition. Further, the *Lactobacillus acidophilus* in the antidiarrheal composition of the present invention can be freeze dried by methods known to those of ordinary skill in the art before being added to the lyophilized ingredients of the present invention. To use the dehydrated composition, one only needs to add the proper amount of water to the dehydrated composition. For example, if the original dose contained 330 ml of water before dehydration, then one would add 330 ml of water to the dehydrated composition before administering it to the patient.

The antidiarrheal composition of the present invention has the general composition shown in Table 1.

Table 1

Ingredient	Dosage Level (per dose)
Water	330 ml
Sodium (as chloride or citrate)	20 to 150 mM/L
Chloride	20 to 150 mM/L
Citrate	10 to 150 mM/L
Potassium (as chloride or citrate)	10 to 100 mM/L
Glucose	10 to 100 mM/L
Bicarbonate	10 to 50 mM/L
Polycarbophil	0.2 to 0.5 g
Carrot powder	10 to 30 g

In addition, approximately 1 to 40 mM/L zinc ion, approximately 8.3 to 16.5 g short-chain glucose polymers, approximately $5x10^9$ CFU to $5x10^{10}$ CFU of *Lactobacillus* GG or an admixture thereof can optionally be added. The electrolyte concentrations shown in the above Table 1 are final concentrations. Thus, it is important to analyze the electrolyte composition of the nutritional substances so the concentrations of the exogenously added electrolytes can be adjusted accordingly. Analysis of the electrolyte composition of the nutritional substance can be performed by procedures well-known to those of ordinary skill in the art.

It is to be understood that these examples describe preparing single doses of the antidiarrheal composition of the present invention and that preparation of large amounts of the composition can be done by proportionately scaling up all ingredient amounts.

The following specific examples will illustrate the invention. It will be appreciated that other examples will be apparent to those of ordinary skill in the art and that the invention is not limited to these specific illustrative examples.

Example 1

The nutritional substance in the antidiarrheal composition of the present invention can be mashed carrots. To prepare the mashed carrots, 500 g. of young carrots are boiled slowly in 1 liter water for about 90 minutes. If necessary, water can be added during the boiling. Thereafter, the carrots are transformed into a puree either by rubbing them through a sieve or with a blender-mixer. Water is added to the puree to bring the total volume to 1 liter.

The carrot puree is then dehydrated either by desiccation or lyophilization and ground into a fine powder. The dehydrated carrot powder is used in preparing the antidiarrheal composition of the present invention.

Example 2

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 2.

Table 2

Ingredient	Dosage Level (per dose)
Water	330 ml
Sodium (as chloride or citrate)	40 mM/L
Chloride	35 mM/L
Citrate	25 mM/L
Potassium (as chloride or citrate)	20 mM/L
Glucose	40 mM/L
Bicarbonate	30 mM/L
Polycarbophil	.33 g
Carrot powder	16.5 g

The ingredients in Table 2 are admixed to form a smooth textured composition suitable for oral administration to a human or animal with diarrhea. It is to be understood that non-dehydrated carrot puree could be used to prepare the antidiarrheal composition of the present invention. The amount of water would have to be appropriately adjusted.

Example 3

The composition of Example 2 wherein the composition is lyophilized to form a ready-to-use composition that can be reconstituted by adding water and mixing.

Example 4

For children between approximately 3 and 6 years of age the oral dosage of the composition described in Example 2 is approximately 0.33 L. to 0.5 L. three times a day or as needed. The dosage should not exceed 1.5 L. in twenty four hours.

Example 5

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 3.

Table 3

Ingredient	Dosage Level (per dose)
Water	330 ml
Sodium (as chloride or citrate)	40 mM/L
Chloride	35 mM/L
Citrate	25 mM/L
Potassium (as chloride or citrate)	20 mM/L
Zinc	5 mM/L
Glucose	40 mM/L
Bicarbonate	30 mM/L
Polycarbophil	.33 g
Carrot powder	16.5 g

The ingredients in Table 3 are admixed to form a smooth textured composition suitable for oral administration to a human or animal with diarrhea.

Example 6

The composition of Example 5 wherein the composition is lyophilized to form a ready-to-use composition that can be reconstituted by adding water and mixing.

Example 7

For children between approximately 3 and 6 years of age the oral dosage of the composition described in Example 5 is approximately 0.33 L. to 0.5 L. three times a day or as needed. The dosage should not exceed 1.5 L. in twenty four hours.

Example 8

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 3 except rice flour is substituted for carrot powder.

Example 9

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 3 except approximately $5x10^9$ CFU to $5x10^{10}$ CFU of *Lactobacillus* GG are added to the mixture.

Example 10

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 3 except rice flour is substituted for carrot powder and approximately $5x10^9$ CFU to $5x10^{10}$ CFU of *Lactobacillus* GG are added to the mixture.

Example 11

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 4.

Table 4

Ingredient	Dosage Level (per dose)
Water	330 ml
Sodium (as chloride or citrate)	40 mM/L
Chloride	35 mM/L
Citrate	25 mM/L
Potassium (as chloride or citrate)	20 mM/L
Zinc	5 mM/L
Glucose	40 mM/L
Bicarbonate	30 mM/L
Polycarbophil	.33 g
Carrot powder	16.5 g
Glucose polymers	2.5 g

Example 12

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 4 except approximately $5x10^9$ CFU to $5x10^{10}$ CFU of *Lactobacillus* GG are added to the mixture.

Example 13

The antidiarrheal composition is prepared using the ingredients and amounts shown in Table 4 wherein the short-chain glucose polymers are two to nine glucose units long, and derived from the controlled hydrolysis of rice.

Example 14

For children between approximately 2 weeks and 3 years of age the oral dosage of the composition described in Example 11 is approximately 0.1 to 0.5 L three times a day or as needed.

It should be understood that the foregoing relates only to a preferred embodiment of the present invention and that numerous modifications or alterations may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

CLAIMS

1. An antidiarrheal composition for use in a human or animal comprising an admixture of:

a. a nutritional substance selected from the group consisting of carrots, maize, millet, sorghum, carob, rice, rice flour, rice water, mashed potatoes and short-chain glucose polymers or admixtures thereof;

b. a pharmaceutically acceptable synthetic fiber such as polycarbophil; and

c. an oral rehydration mixture selected from the group consisting of monosaccharides and electrolytes or admixtures thereof.

2. The antidiarrheal composition of Claim 1, wherein the composition is sterilized.

3. The antidiarrheal composition of Claim 1, wherein the composition is dehydrated.

4. The antidiarrheal composition of Claim 1, wherein the composition is a rehydratable ready to use composition.

5. The antidiarrheal composition of Claim 1, further comprising an effective concentration of *Lactobacillus*.

6. A method of treating a human or animal with diarrhea comprising the step of orally administering to the human or animal with diarrhea an effective amount of a composition of a nutritional substance selected from the group consisting of carrots, maize, millet, sorghum, carob, rice, rice flour, rice water, mashed potatoes, and short-chain glucose polymers or admixtures thereof, a pharmaceutically acceptable synthetic fiber, and an oral rehydration mixture selected from the group consisting of monosaccharides and electrolytes.

7. The method of treating diarrhea of Claim 6, further comprising an effective concentration of *Lactobacillus*.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/02445

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 9/68; A61K 35/78 A23G 3/30 A61K 31/70

US CL.: 424/78; 424/195.1; 426/6; 514/50; 514/867

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
US	424/78; 424/195.1; 426/6; 514/50; 514/867

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	The Lancet, August 19, 1989, (MOLLA et al.) "Food-Based Oral Rehydration Salt Solution for Acute Childhood Diarrhoea". pages 429-431.	1-7
Y	Handbook of Nonpresciption Drugs June 14, 1977 American Pharmaceutical Association, 5th Edition, pages 26,31 and 33-35.	1-7
Y	Chemical Abstracts, Volume 101, No. 22, issued 30 November 1984 (Columbus Ohio, USA, Nisshin Flour Milling Co., "Antidiarrhea compositions containing minerals and sodium acrylate polymers". see page 378, column 2, the abstract No. 198189;, JP 59-65016 13 April 1984	1-7

* Special categories of cited documents:

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13 MAY 1991	30 MAY 1991
International Searching Authority	Signature of Authorized Officer
ISA/US	INTERNATIONAL DIVISION KEVIN E. WEDDINGTON

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